952,802

PATENT SPECIFICATION

NO DRAWINGS

952,802

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International Classification:—C 07 c, d

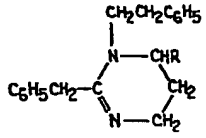
COMPLETE SPECIFICATION

New Tetrahydropyrimidines of Therapeutic Value

We, AYERST, MCKENNA & HARRISON LIMITED, a Canadian Company, of 1025 Laurentien Boulevard, Saint Laurent, Province of Quebec, Canada, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to antihistaminics and bronchodilators.

It has been found that 1-(beta-phenyl)-2-benzyl-1,4,5,6-tetrahydropyrimidine and its 6-methyl homologue which together may be represented by the formula:



and their acid addition salts, where R is hydrogen atom or a methyl group have useful bronchodilator and anti-histaminic properties. Salts for clinical use must, of course, be pharmacologically acceptable and, for this purpose, the hydrohalide salts are preferred as they may be administered orally, by subcutaneous injection, or as aerosols.

When administered orally, subcutaneously, or as aerosols, the anti-histaminic activity of the active compounds of the invention may be demonstrated *in vivo* by the guinea pig aerosol test described by C. H. Siegmund [J. Pharm. Exp. Therap. vol. 90, p. 254 (1947)], and *in vitro* by the Magnus test on the isolated guinea pig ileum. Their bronchodilator activity may be shown in the cat using the test method of Konzett [Arch. fiir Exper. Pathol. Pharmakol. vol. 195, p. 71 (1940)], and by the guinea pig aerosol test mentioned above.

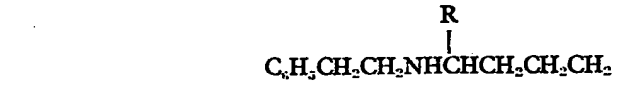
An advantage of the active substances of the invention is that they do not act as sympathommimetic amines and their salts, as may readily be demonstrated in tests on the spontaneous activity of the rat uterus or the guinea pig ileum. Neither do they cause the damage to the heart characteristic of the catechol amines, no significant effect on heart rate or blood pressure being demonstrable in the dog, nor any evidence of tachycardia. Other advantages are that the substances cause neither stimulation nor depression of the central nervous system, and that they possess a long duration of bronchodilator activity after oral administration.

For use as pharmacologically active substances, the compounds of this invention in the form of their pharmacologically acceptable salts, preferably the hydrohalide salts, may be compounded in a known manner with pharmaceutical carriers to form novel compositions. Such carriers may for example consist of starch, lactose, aluminium and magnesium steerates, with other functional agents as may be desired. The mixtures may be prepared and granulated, ground, and pressed into tablets in the usual manner. For subcutaneous or aerosol use the active material may be put up in sterile aqueous isotonic solution.

In accordance with a further feature of the invention the tetrahydropyrimidines

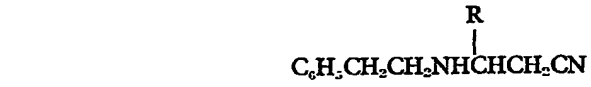
[*Price 4s. 6d.*]

of the invention are prepared by reacting a diamine of the formula:



where R is hereinbefore defined with phenylacetic acid, a lower alkyl phenylacetate or phenylacetonitrile.

The aforesaid diamines may be prepared by reduction of a nitrile of the formula:



where R is as hereinbefore defined. These nitriles may be prepared by the reaction of beta-phenethylamine with acrylonitrile or 3-butenenitrile.

The tetrahydro pyrimidine of the invention where R is hydrogen may also be prepared by the reaction of 2-benzyltetrahydropyrimidine with a beta-phenethyl halide.

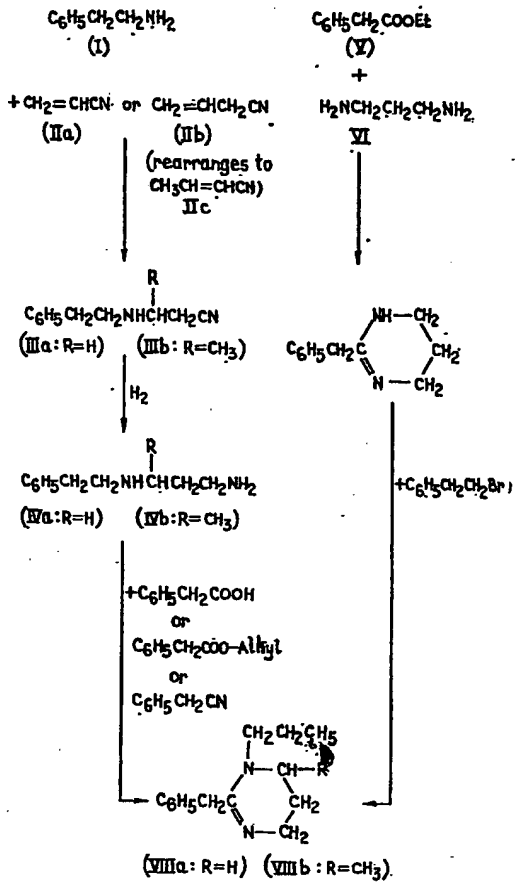
Preferred preparation procedures are as follows:

Beta-phenethylamine (1) is heated to reflux with acrylonitrile (IIa) to obtain 3-(beta-phenethylamino)propionitrile (IIIa). The latter may be reduced either with lithium aluminium hydride or with hydrogen in the presence of Raney Nickel and ammonia to yield 3-(beta-phenethylamino)propionylamine (IVa). The latter diamine (IVa) may then be reacted either with phenylacetic acid, or with ethyl phenylacetate, or with phenylacetonitrile to yield 1-(beta-phenethyl)-2-benzyl-1,4,5,6-tetrahydropyrimidine (VIIIa) which may then be converted to one of its pharmacologically acceptable salts.

Alternatively, ethyl phenylacetate (V) may be reacted under pressure with 1,3-propanediamine (VI) to yield 2-benzyl-1,4,5,6-tetrahydropyrimidine (VII). The latter may then be refluxed in isopropanol solution with a beta-phenethylhalide to yield 1-(beta-phenethyl)-2-benzyl-1,4,5,6-tetrahydropyrimidine (VIIIa), as the hydrohalide salts.

If 1-(beta-phenethyl)2-benzyl-6-methyl-1,4,5,6-tetrahydropyrimidine is the end product desired, beta-phenethylamine (1) is reacted with 3-butenenitrile (IIb) in the presence of an organic base such as benzyltrimethyl ammonium hydroxide (Triton B, 'Triton' is a Registered Trade Mark) as a catalyst. In the course of that reaction 3-butenenitrile re-arranges to crotonitrile (IIc) and the reaction product is 3-(beta-phenethylamino)- butyronitrile (IIIb). Reduction of the latter with lithium aluminium hydride gives the corresponding diamine, 3-(beta-phenethylamino)-butylamine (IVb). The diamine (IVb) is transformed to its bis-*p*-toluenesulphonic salt and can then be reacted with phenylacetonitrile according to the method of Oxley & Short (J. Chem. Soc., 1950, pp. 859—864) to yield 1-(beta-phenethyl)-2-benzyl-6-methyl-1,4,5,6-tetrahydropyrimidine (VIIIb), which may then be converted to one of its pharmacologically acceptable acid addition salts.

The above processes may be exemplified by the following reaction scheme.



The following Examples III, VI and VIII illustrate the invention; the remaining Examples describe the preparation of various starting materials.

EXAMPLE I.

3-(beta-phenethylamino)propionitrile (IIIa).

208.12 g. of beta-phenethylamine were added portionwise to 183.5 g. of acrylonitrile and the mixture was left standing at room temperature for twentyfour hours. The solution was then heated to reflux for two hours. The excess acrylonitrile was evaporated under reduced pressure and the residue distilled under high vacuum, b.p. 123—129° C. at 0.04 mm. A sample of the hydrochloride salt of this material was prepared for analytical purposes, m.p. 181—184° C.

Calc. for $C_{11}H_{14}N_2.HCl$: Cl, 16.83
Found : Cl, 16.51%

EXAMPLE II.

3-(beta-phenethylamino)propylamine (IVa).

A suspension of 9.5 g. of lithium aluminium hyddride in 500 cc. of dry A.R. ether was prepared 41.9 g. of 3-(beta-phenethylamino)propionitrile (IIIa) dissolved in 100 cc. of dry ether were added dropwise maintaining the temperature of the reaction mixture below 10° C. The cooling bath was taken away and the mixture was stirred at room temperature for thirty minutes. The reaction mixture was cooled again to 10° C. and 10 ml. of water were added dropwise followed by 25 ml. of a 25% sodium hydroxide solution and finally by 10 ml. of water. The inorganic salts were filtered on a Buchner funnel and washed with acetone. The solvent was evaporated under reduced

pressure and the residue distilled under vacuum, b.p. 155—163° C. at 10 mm. A sample of the hydrochloride salt of this material was prepared by analytical purposes, m.p. 285—291° C.

Calcd. for $C_{11}H_{18}N_2.2HCl$: Cl, 28.23%
Found : Cl, 28.03%

Alternatively, a mixture of 500 g. (2.88 moles) of 3-(beta-phenethylamino)propionitrile, 2,000 ml. of methanol, 374 grams (22 moles) of ammonia and 50 g. of Raney Nickel catalyst was put in a stainless steel bomb. The material was reduced at a pressure of 300 p.s.i. and at a temperature of 40° C. for a period of forty-three hours. The catalyst was filtered off, the solvent evaporated under reduced pressure, and the product distilled under vacuum to yield 3-(beta-phenethylamino)propylamine, boiling at 97—100° C. at 0.5 to 0.7 mm.

Example III.

1-(beta-phenethyl)-2-benzyl-1,4,5,6-tetrahydropyrimidine (VIIIa).

32.9 g. of 3-(beta-phenethylamino)propylamine (IVa) and 24.5 g. of phenylacetic acid were heated at 240° C. for thirty minutes and the water was distilled off as it was formed. The product was then distilled under high vacuum, b.p. 165—171° C. at 0.08 mm. The hydrobromide salt, m.p. 186—188° C., was prepared by conventional means

Calcd. for $C_{19}H_{22}N_2.HBr$: Br, 22.24%
Found : Br., 23.07%

Alternatively, 30.2 g. of 3-(beta-phenethylamino) propylamine (IVa) and 25.1 g. of ethyl phenylacetate were heated at 240—245° C. for thirty minutes distilling off the ethanol as it was formed. The reaction mixture was then cooled and the thick oily material was distilled under high vacuum, b.p. 160—175° C. at 0.07 mm. The hydrobromide salt, m.p. 181—184° C., was prepared as above.

In an additional alternative procedure, 1,120 g. (4.46 moles) of 3-(beta-phenethylamino)propylamine dihydrochloride, 795 g. (4.46 moles) of the free base of the above diamine, and 1,043 g. (8.92 moles) of phenylacetonitrile were stirred and heated gradually to a temperature of 200° C. The reaction mixture was maintained at that temperature for an additional two hours. The mixture was then dissolved in 6 litres of water, made alkaline with sodium hydroxide and the product extracted with benzene. The benzene extract was washed with water, dried over sodium sulphate and treated with anhydrous hydrogen chloride. The product was recrystallised from isopropanol to yield 1-(beta-phenethyl)-2-benzyl-1,4,5,6-tetrahydropyrimidine hydrochloride.

Example IV.

3-(beta-phenethylamino) butyronitrile (IIIb).

67.09 g. (1.0 mole) of 3-butenenitrile (IIb) and 121 g. (1.0 mole) of beta-phenethylamine (I) were dissolved in 200 cc. of methanol, 4 ml. of Triton B were added dropwise to the reaction mixture which was stirred vigorously for a period of one hour. The mixture was then allowed to stand at room temperature overnight and then heated to reflux for a period of four hours .The methanol was evaporated under reduced pressure and the oily residue was dissolved in 300 cc. of benzene. The benzene solution was washed with water (4 × 50 cc.) and dried over sodium sulphate. The benzene was evaporated under reduced pressure and the residue distilled under high vacuum, b.p. 127—130° C. at 0.08 mm. A sample of the hydrochloride salt of this material was prepared for analytical purposes.

Calcd. for $C_{12}H_{16}N_2.HCl$: Cl, 15.78%
Found : Cl, 15.87%

Example V.

3-(beta-phenethylamino) butylamine (IVb).

A suspension of 19 g. (0.50 mole) of lithium aluminium hydride in 500 cc. of ether was prepared. 90 g. (0.48 mole) of 3-(beta-phenethylamino) butyronitrile (IIIb) dissolved in 200 cc. of ether were added dropwise maintaining the temperature of the reaction mixture below 10° C. throughout the addition. The reaction mixture was then allowed to reach room temperature gradually and then stirred for an additional thirty

minutes. The reactants were then cooled to a temperature of 10° C. and 20 cc. of water followed by 40 cc. of 25% NaOH in water and an additional 20 cc. of water were added dropwise. The inorganic salts were filtered off, the ether was evaporated under reduced pressure and the remaining liquid distilled under vacuum, b.p. 148° C. at 10 mm. A sample of the hydrochloride salt of this material was prepared for analytical purposes, m.p. 224—225° C.

Calcd. for $C_{12}H_{20}N_2.2HCl$: Cl, 26.74%
Found : Cl, 26.65%

EXAMPLE VI.

1-(beta-phenethyl)-2-benzyl-6-methyl-1,4,5,6-tetrahydropyrimidine (VIIIb).

15.7 g. of 3-(beta-phenethylamino) butylamine (IVb) were dissolved in 50 cc. of water and a solution of 30 g. of *p*-toluenesulphonic acid in 100 cc. of water was added. The water was then evaporated to dryness under reduced pressure and the remaining oil crystallized on standing. The solid mass was triturated with ether and the crystals filtered on a Buchner funnel to obtain the crude bis-*p*-toluenesulphonic acid salt of 3-(beta-phenethylamino) butylamine. 24.5 g. (0.05 mole) of the above salt, 9.6 g. (0.05 mole) of 3-(beta-phenethylamino) butylamine and 5.85 g. (0.05 mole) of phenylacetonitrile were mixed and heated at 200° C. for a period of nine hours. The green mass was cooled, treated with 20% sodium hydroxide in water and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulphate and evaporated under reduced pressure. The residue was distilled under high vacuum, b.p. 177—180° C. at 0.04 mm. The hydrochloride salt, m.p. 135—137° C. was prepared by conventional means.

Calcd. for $C_{20}H_{24}N_2.HCl$: N, 8.52; Cl, 10.78%
Found : N, 8.32; Cl, 10.50%

EXAMPLE VII.

2-Benzyl-1,4,5,6-tetrahydropyrimidine (VII).

129.5 g. of 1,3-propanediamine (VI) and 94.5 g. of ethyl phenylacetate (V) were heated at 100° C. for twelve hours in an autoclave. The reaction mixture was then filtered on a Buchner funnel and the filtrate distilled under vacuum, b.p. 176—182° C. at 8.0 mm. This material crystallised on standing at room temperature. It was recrystallised from acetone, m.p. 115—118° C.

Calcd. for $C_{11}H_{14}N_2$: C, 75.82%; H, 8.10%; N, 16.08%
Found : C, 75.93%; H, 8.02%; N, 15.72%

EXAMPLE VIII.

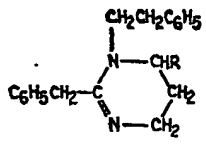
1-(beta-phenethyl)-2-benzyl-1,4,5,6-tetrahydropyrimidine (VIIIa) hydrabromide.

3.0 g. of benzyl-1,4,5,6-tetrahydropyrimidine (VII) were dissolved in 25 ml. of isopropanol. 1.8 g. of sodium carbonate and 3.15 g. of beta-phenethylbromide were added to the reaction mixture which was stirred and heated to reflux for a period of eighteen hours. The solvent was evaporated under reduced pressure and the remaining oily material was crystallised and recrystallised from isopropanol, m.p. 185—186° C.

Calcd. for $C_{15}H_{22}N_2.HBr$: C, 63.50%; H, 6.45%; N, 7.80%, Br, 22.24%
Found : C, 63.84%; H, 6.32%; N, 7.34%; Br, 22.41%

WHAT WE CLAIM IS:—

1. A tetrahydropyrimidine of the formula:



or acid addition salt thereof, where R is a hydrogen atom or a methyl group.

2. 1-(Beta-phenethyl)-2-benzyl-1,4,5,6-tetrahydropyrimidine hydrochloride or hydrobromide.

3. 1-(Beta-phenethyl)-2-benzyl-6-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride.

4. Process for the preparation of a tetrahydropyrimidine as claimed in claim 1 which comprises reacting a diamine of the formula:

with phenylacetic acid, a lower alkyl phenylacetate, or phenylacetonitrile.

5. Process for the preparation of a tetrahydropyrimidine as claimed in claim 1 (where R is hydrogen) which comprises reacting 2-benzyl-tetrahydropyrimidine with a beta-phenethyl halide.

6. Process according to claim 4 substantially as described in Example III or VI.

7. Process according to claim 5 substantially as described in Example VIII.

8. A tetrahydropyrimidine as claimed in claim 1 when prepared by the process claimed in claim 4, 5, 6 or 7.

9. A pharmaceutical composition comprising one or more tetrahydropyrimidines as claimed in any of claims 1 to 3 or 8 or acid addition salt thereof in association with a pharmaceutical carrier.

10. A pharmaceutical composition as claimed in claim 9 substantially as described.

J. A. KEMP & CO.,
Chartered Patent Agents,
14 South Square, Gray's Inn,
London, W.C.1.

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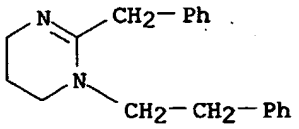
L18 ANSWER 135 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1964:424707 CAPLUS
DN 61:24707
OREF 61:4162c-e
TI Tetrahydropyrimidines as antihistamines and bronchodilators
PA Ayerst, McKenna & Harrison, Ltd.
SO 6 pp.
DT Patent
LA Unavailable

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 952802		19640318	GB	
	CA 706890			CA	
PRAI	CA		19610302		

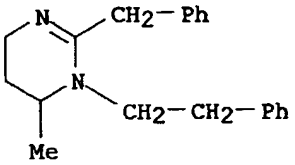
AB C6H5CH2CH2NHCH2CH2CH2NH2 (I) or C6H5CH2CH2NHCH(CH3)CH2CH2NH2 (II) was treated with phenylacetic acid (III) or alkyl phenylacetate or phenylacetonitrile. Thus, 32.9 g. I and 24.5 g. of III were heated at 240° for 30 min., and the H2O dist. off. IV was obtained by distillation, b0.08 165-171° (m.p. of the HBr salt, 186-8°). V was obtained with II as starting material. Both IV and V showed antihistamine properties by the guinea pig aerosol test or by the Magnus test on the isolated guinea pig ileum. Bronchodilator activity was shown in the cat by Konzelt's method and in the guinea pig aerosol test.

IT **94308-50-6**, Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-1-phenethyl- **94679-12-6**, Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-6-methyl-1-phenethyl- **98823-26-8**, Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-1-phenethyl-, hydrobromide **99098-61-0**, Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-6-methyl-1-phenethyl-, hydrochloride
(as antihistamine and bronchodilator)

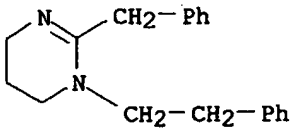
RN 94308-50-6 CAPLUS
CN Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-1-phenethyl- (7CI) (CA INDEX NAME)



RN 94679-12-6 CAPLUS
CN Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-6-methyl-1-phenethyl- (7CI) (CA INDEX NAME)

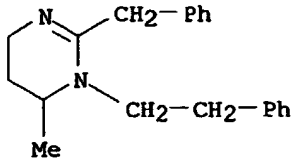


RN 98823-26-8 CAPLUS
CN Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-1-phenethyl-, hydrobromide (7CI) (CA INDEX NAME)



● HBr

RN 99098-61-0 CAPLUS
CN Pyrimidine, 2-benzyl-1,4,5,6-tetrahydro-6-methyl-1-phenethyl-, hydrochloride (7CI) (CA INDEX NAME)



● HCl